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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/023,232	02/13/1998	ANN MONOSOV	312762001530	6662

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EXAMINER	
BECKERLEG, ANNE M	

ART UNIT	PAPER NUMBER
1632	19

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/023,232	Applicant(s) MONOSOV ET AL.	
	Examiner Anne M Beckerleg	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 November 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18,20-25,27,28,30-37,42-49 and 54-61* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18,20-25,27,28,30-37,42-49 and 54-61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *16* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicant's amendment received on 11/21/01 has been entered. Claims 19, 26, 29, 38-41, 50-53, and 62-65 have been canceled. Claims 1-18, 20-25, 27-28, 30-37, 42-49, and 54-61 are pending in the instant application. Please note that prosecution has been reopened in this case in view of new grounds of rejection presented below. As such, the finality of the previous office is withdrawn. An action on the merits follows.

The rejection of claims 19, 26, 29, 38-41, 50-53, and 62-65 under 35 U.S.C. 112, first paragraph, has been withdrawn in view of applicant's cancellation of the claims.

The rejection of claims 1-13, 15, 17, 19-20, 22, 24, 26-29, and 31-65 under 35 U.S.C. 103 over Wang et al. in view of McLemore et al. and Otto et al. has been withdrawn in view of applicant's cancellation of the claims or in view of new grounds of rejection under 35 U.S.C. 103, see below.

The rejection of claims 14, 16, 21, and 23 under 35 U.S.C. 103 over Wang et al., McLemore et al., Otto et al. and Giovanella et al. has been withdrawn in view of new grounds of rejection under 35 U.S.C. 103, see below.

The rejection of claims 18 and 25 under 35 U.S.C. 103 over Wang et al., McLemore et al., Otto et al. and Reddy et al. has been withdrawn in view of new grounds of rejection under 35 U.S.C. 103, see below.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-13, 15, 17-18, 20, 22, 24, 27-28, 30-37, 42-49, and 54-61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kyriazis et al. (1981) Canc. Res., Vol. 41, 3995-4000 in view of Otto et al. (1985) J. Urol., Vol. 134, 170-174, Wang et al. (1982) Exp. Cell. Biol., Vol.

50, 330-331, and McLemore et al. (1987) Cancer Research, Vol. 47(19), 5132-5140. The applicant claims nude mouse, nude rodent, immunodeficient rodent, or non-human mammal models of human neoplastic disease characterized by having intact human neoplastic tissue of at least $1mm^3$ transplanted orthotopically, and having sufficient immuno-deficiency to allow said tissue to grow and mimic the progression of the neoplastic disease in the human donor, wherein said tissue is selected from breast, ovarian or lung (pleural) tissue, and methods of generating said models comprising orthotopic transplantation of said tissue. The applicant is reminded that, "[e]ven though product - by process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product - by - process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." In re Thorpe , 227 USPQ 964, 966 (Fed. Cir. 1985). MPEP 2113.

Kyriazis et al. teaches the transplantation of numerous different kinds of intact human tumors pieces measuring approximately 0.3-0.4 cm into nude mice resulting in the formation of consistent levels of metastases in lung and lymph nodes (Kyriazis et al., page 3995, column 2, and page 3996, Table 1). Tumors tested by Kyriazis include bladder, breast, colon, laryngeal, and pancreatic tumors. Kyriazis et al. further teaches that the observed malignant behavior of the human tumors in nude mice recapitulates the biological characteristics of the tumor in humans (Kyriazis et al., page 3995). Otto et al. supplements Kyriazis et al. by teaching that the growth of

human renal cell carcinoma embedded in renal tissue from nephrectomized patients that had been transplanted into nude mice correlated well with the clinical course of the patients (Otto et al., page 170).

Neither Kyriazis et al. nor Otto et al. specifically teach the orthotopic transplantation of human tissue to nude mice. Wang et al. supplements Kyriazis and Otto by teaching that the orthotopic transplantation of colonic tumors, maintained in nude mice, into the colonic wall of naive nude mice results in growth and metastasis of the colonic tumors which mimics the pattern of metastasis observed in the original human patients (Wang et al., page 331, abstract). McLemore et al. also supplements Kyriazis and Otto by teaching an athymic nude mouse model for human lung cancer, wherein nude mice receive orthotopic transplantation of several different human lung carcinoma cells lines intrabronchially (McLemore et al., page 5133, column 2 paragraphs 2-4). McLemore et al. further provides motivation for using orthotopic transplantation versus subcutaneous transplantation of human tumors in nude mice by demonstrating that mice transplanted intrabronchially with lung tumor cells demonstrated increased rates of growth and metastases than those transplanted subcutaneously (McLemore et al., page 5132, abstract, and 5133, Table 1).

Thus, in view of the motivation provided by McLemore et al. and Wang et al. that orthotopic implantation of tumor cells results in the growth of human tumors in mice that mimics the growth patterns of the human tumors in human patients and that human tumors implanted orthotopically demonstrate increased rates of growth compared to tumors transplanted

subcutaneously, it would have been *prima facie* obvious to the skilled artisan to substitute orthotopic implantation for subcutaneous implantation in the method of generating a nude mouse model of human cancer taught by Kryiazis et al. and Otto et al. Furthermore, based on the teachings of Otto et al. and Kryiazis et al. that intact tumor tissue maintains growth and morphological characteristics in the nude mouse, and the teachings of Wang et al. and McLemore et al. that orthotopic transplantation in nude mice versus subcutaneous transplantation more closely mimics the growth and metastases of human tumors in patients, the skilled artisan would have had a reasonable expectation of success in generating and using a nude mouse model for human neoplastic disease which mimics the growth and metastasis of the human tumors in patients characterized by orthotopically transplanted intact human colon, lung, or breast tissue.

In addition, as the art of record teaches that many different types of tumor tissue, including colonic, lung, renal, pancreatic, laryngeal, and bladder tissue, can be transplanted orthotopically into mice to generate a mouse model for human neoplastic disease, it would have been *prima facie* obvious to the skilled artisan to generate a nude mouse model for any type of human cancer, including ovarian cancer, by implanting the human neoplastic tissue into the analogous murine tissue. Therefore, in view of the high level of surgical skill in transplanting tissue into mice at the time of filing, the motivation to generate mouse models for many different kinds of human tumors by orthotopically transplanting human tumor tissue to nude or immunodeficient mice as provided by Wang et al., McLemore et al., and Otto et al., the skilled artisan would have had a reasonable expectation of success in implanting neoplastic human

ovarian tissue into murine ovarian tissue in order to produce a murine model for human ovarian neoplastic disease.

Applicant's arguments regarding the teachings of Wang et al., McLemore et al., and Otto et al. have been addressed in as much as they relate to the present rejection of record. The applicant argues that the applicant's results as represented by several post-filing publications demonstrate the generation of metastases in 100% of the tested mice. As such, the applicant argues that the reliability of the instant methods to produce metastases of human tumors in nude mice represents an unexpected result over the teachings of the prior art. However, the claims do not recite any particular limitation regarding the frequency with which mice produced using the instant methodology generate metastases. The claims do not recite that the methods have to be 100% effect, or recite any specific limitation regarding the metastatic growth patterns of the implanted tumors or the time course over which the disease course is to be followed. The claims simply recite that the implanted tumor "mimics the progression of the neoplastic disease in the rodent". Wang explicitly teaches that the disclosed nude mouse model does just that. Further, Kryiazis et al. clearly demonstrates that the implantation of intact pieces of human tumors into nude mice consistently generates metastases. In addition, in regards to claims directed to the nude mouse model itself, the efficiency of the method of making the mouse are not relevant to the patentability of the claims as long as the mouse itself is taught or suggested by the prior art. See In re Thorpe as cited above. Thus, applicant's arguments regarding a 100% success rate in generating nude mice with metastatic human tumors are unpersuasive.

Claims 14, 16, 21, and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kyriazis et al. (1981) Canc. Res., Vol. 41, 3995-4000 in view of Otto et al. (1985) J. Urol., Vol. 134, 170-174, Wang et al. (1982) Exp. Cell. Biol., Vol. 50, 330-331, and McLemore et al. (1987) Cancer Research, Vol. 47(19), 5132-5140 as applied to claims 1-13, 15, 17-18, 20, 22, 24, 27-28, 30-37, 42-49, and 54-61 above, and further in view of Giovanella et al. (1984) Exp. Cell. Biol., Vol. 52, 76-79. The applicant claims a nude or immunodeficient rat model for human neoplastic disease characterized by having intact human neoplastic tissue of at least $1mm^3$ transplanted orthotopically and having sufficient immuno-deficiency to allow said tissue to grow and mimic the progression of the neoplastic disease in the human donor, and methods of generating said models comprising orthotopic transplantation of said tissue.

As discussed in the preceding rejection, the combined teachings of Kyriazis et al. in view of McLemore et al., Otto et al., and Wang provide the methods and motivation for making and using a nude mouse model for human cancer comprising the orthotopic transplantation of intact human breast, colon, pancreatic, or lung tissue. Wang, McLemore, Kyriazis and Otto all teach nude mouse models. Giovanella et al. teaches that human tumors can be transplanted and grown in either nude mice or rats (Giovanella et al., page 76, Tables I and II). Giovanella et al. also teaches that human tumors grow more rapidly in nude rats than in nude mice (Giovanella et al., page 77 Figures 1-2). Thus, it would have been *prima facie* obvious to the skilled artisan to substitute nude rats for nude mice in a nude rodent model for human neoplastic disease in order to

decrease the time required to conduct experiments. Further, based on the teachings of Giovanella et al., that human tumors grow in rats, the skilled artisan would have had a reasonable expectation of success in using a nude rat to generate a model for human cancer comprising the orthotopic transplantation of intact tumor tissue.

The applicant has not presented any specific arguments regarding the teachings of Giovanella. Arguments directed to McLemore, Wang, and Otto have been addressed above.

Claims 18 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kyriazis et al. (1981) Canc. Res., Vol. 41, 3995-4000 in view of Otto et al. (1985) J. Urol., Vol. 134, 170-174, Wang et al. (1982) Exp. Cell. Biol., Vol. 50, 330-331, and McLemore et al. (1987) Cancer Research, Vol. 47(19), 5132-5140 as applied to claims 1-13, 15, 17-18, 20, 22, 24, 27-28, 30-37, 42-49, and 54-61 above, and further in view of Reddy et al. (1987) Cancer Res., Vol. 47 (9), 2456-2460. The applicant claims an immunodeficient SCID mouse model for human neoplastic disease characterized by having intact human neoplastic tissue of at least $1mm^3$ transplanted orthotopically and having sufficient immuno-deficiency to allow said tissue to grow and mimic the progression of the neoplastic disease in the human, and methods of generating said model comprising orthotopic transplantation of said tissue.

As discussed in the preceding rejection, the combined teachings of Kyriazis et al. in view of McLemore et al., Otto et al., and Wang et al. provide the methods and motivation for making and using a nude mouse model for human cancer comprising the orthotopic transplantation of

intact human colon or lung tissue. Wang, McLemore, Kyriazis and Otto all teach nude mouse models. Reddy et al. teaches a SCID mouse model of human lung cancer comprising the transplantation of human lung tumor cells to SCID mice (Reddy et al., page 2456, abstract). Reddy et al. also provides motivation for substituting the SCID mouse for the nude mouse by teaching that 100% of the transplanted mice developed tumors, and that, " mice with this severe combined immunodeficiency represent a new and viable model for propagating human tumors and for evaluating the efficacy of novel drug delivery protocols in the treatment of cancer" (Reddy et al., abstract). Thus, based on the teachings of Reddy et al., it would have been *prima facie* obvious at the time of filing to substitute a SCID mouse for the nude mice taught by Wang, McLemore, and Otto, and the skilled artisan would have had a reasonable expectation of success in both generating and using a SCID mouse model for human neoplastic disease characterized by orthotopic transplantation of intact human tumor tissue.

The applicant has not presented any specific arguments regarding the teachings of Reddy. Arguments directed to McLemore, Wang, and Otto have been addressed above.

No claims are allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Beckerleg, Ph.D., whose telephone number is (703) 306-9156. The examiner can be reached Mon- Fri from 10:30-7:00. If the examiner is not available, the examiner's supervisor,

Deborah Clark, can be reached at (703) 305-4051. General inquiries should be directed to the group receptionist whose phone number is (703) 308-0196. The technology center fax number is (703) 308-4242, the examiner's direct fax number is (703) 746-7024.

Dr. A.M.S. Beckerleg

A.M.S. BECKERLEG.
PATENT EXAMINER